# Troglitazone, an Insulin Action Enhancer, Improves Glycaemic Control and Insulin Sensitivity in Elderly Type 2 Diabetic Patients

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**The management of Type 2 diabetes mellitus with currently available oral agents may be complicated in the elderly by an increased frequency of side-effects. The effects of troglitazone, an insulin action enhancer, were studied in elderly patients with Type 2 diabetes in a double-blind, parallel-group, placebo-controlled trial. A total of 229 patients (41 % male), mean age 75 (range 69–85) years, with two fasting capillary blood glucose values $\geq$7 and $\leq$15 mmol l$^{-1}$ (and within 4.0 mmol l$^{-1}$ of each other) and previously treated with either diet alone (30 %) or oral hypoglycaemic agents, were randomized to placebo or troglitazone 400 mg once daily or 200 mg twice daily, or 800 mg once daily or 400 mg twice daily, for 12 weeks. After 12 weeks' treatment, fasting serum glucose was significantly lower in troglitazone-treated patients (troglitazone, adjusted geometric mean 9.4–10.4 mmol l$^{-1}$ vs placebo 12.7 mmol l$^{-1}$, $p<0.001$). Adjusted geometric mean fructosamine was also lower in troglitazone-treated patients by 5 to 15 % compared to placebo ($P<0.05$ at all doses except 400 mg od). There was no significant difference between troglitazone doses for improvement in glycaemic control. Troglitazone lowered adjusted geometric mean fasting plasma insulin by 27–34 % compared to placebo ($P<0.001$) and insulin sensitivity (HOMA-S) improved by 9–15 % in all troglitazone dose groups ($p<0.001$). Troglitazone also lowered serum non-esterified fatty acids and triglyceride. Adverse event incidence in troglitazone-treated patients was similar to that in patients treated with placebo. No weight gain or symptomatic hypoglycaemia was recorded at any of the doses studied. Troglitazone is effective and well tolerated in elderly patients with Type 2 diabetes mellitus, providing improved glycaemic control in the absence of weight gain.** 

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## Introduction

The management of Type 2 diabetes mellitus (DM) in the elderly poses special problems. Diet and exercise are fundamental to management, but major lifestyle changes are often not practical as many elderly patients also suffer from other chronic conditions such as heart disease and arthritis. Oral hypoglycaemic agents are, therefore, often required to control hyperglycaemia. Currently available drugs are not ideal.[1] Sulphonylureas are associated with a higher risk of hypoglycaemia in elderly compared with younger patients.[1,2] Metformin is associated with a higher risk of side-effects in the elderly, although it can be a relatively safe and effective agent in older subjects provided that the contraindications are strictly observed and the patients monitored. Acarbose, an $\alpha$-glucosidase inhibitor, may offer some advantages in elderly people, for example lack of hypoglycaemia or weight gain; however, its effective dose is limited by gastrointestinal side effects.[3] There is, therefore, a need for other safe and effective oral agents for management of Type 2 diabetes in the elderly.

Troglitazone is a thiazolidinedione that lowers blood glucose primarily by enhancing insulin action at its target tissues.[4–6] Previous studies in small numbers of subjects with Type 2 diabetes have shown it to be effective in reducing both fasting and postprandial hyperglycaemia, while at the same time reversing other metabolic

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abnormalities such as insulin resistance and dyslipidaemia.[7–9] In recent large European multicentre studies in patients with Type 2 diabetes, where daily doses in the range 10–800 mg were investigated, troglitazone was both effective and well tolerated.[10–11] These studies have suggested that the therapeutic dose range of troglitazone for the management of Type 2 diabetes is 200–600 mg taken once daily. These studies did not, however, include patients aged over 70 years. The metabolic profiles and pharmacokinetic parameters of troglitazone and its metabolites have been compared in young and elderly healthy volunteers and have shown no clinically relevant difference after 14 days' administration of 400 mg twice daily.[12]

We report the results of a European multicentre study conducted to evaluate the safety and efficacy of troglitazone 400 and 800 mg/day in elderly patients with Type 2 diabetes.

## Patients and Methods

### *Patients*

Patients with Type 2 diabetes aged between 69 and 85 years who had been treated with diet alone or diet and oral hypoglycaemic agents for at least the previous 3 months were studied. Exclusion criteria included a history of myocardial infarction or angina or uncontrolled hypertension (>165/95 mmHg), cerebrovascular disease, significant renal or liver disease, symptomatic diabetic neuropathy requiring treatment and recent gross weight change.

### *Study Design*

This was a randomized, double-blind, parallel-group, placebo-controlled trial, conducted in 34 centres in seven European countries. The approval of the regulatory authorities in each country (where appropriate) and the local ethics committee for each centre was obtained. The study was conducted in accordance with the Declaration of Helsinki, and witnessed, informed consent was obtained from each patient.

At the first visit, patients on oral hypoglycaemic agents stopped their regular medication. During a run-in period of 2–4 weeks for those previously treated by diet only, and 3–4 weeks for those previously treated with oral hypoglycaemic agents, fasting capillary blood glucose levels were measured weekly in the clinic. At the end of the run-in period, patients were randomized to study medication if the last two consecutive blood glucose measurements were $\geq$7.0 mmol $l^{-1}$ and $\leq$15.0 mmol $l^{-1}$ and within 4.0 mmol $l^{-1}$ of each other. Patients were randomly allocated to treatment with troglitazone at doses of 400 mg once daily or 200 mg twice daily, or 800 mg once daily or 400 mg twice daily, or placebo, for 12 weeks. The treatment administered was predetermined by a randomization code generated by computer programme in balanced blocks of 10 prior to the start of the study. Centres were allocated one or more blocks of ten. Codes were assigned to the patient at the baseline visit and were allocated consecutively by the investigator. Patients were asked to take the study medication with, or up to 30 min after, breakfast and the evening meal. At this visit baseline assessments were made. The randomized patients were reassessed at 1, 2, 4, 6, 8, and 12 weeks after baseline assessment and again 10–14 days after treatment completion or withdrawal. Compliance was checked by tablet counting. Standard dietary advice was given to all patients with regard to the spreading of carbohydrate load, increasing dietary fibre, the reduction of fat and limitation of sugar and alcohol intake.

### *Measurements*

Measurements included fasting serum glucose, $HbA_{1c}$, fructosamine, C-peptide, insulin, and serum lipid profile (total cholesterol, LDL-cholesterol, HDL-cholesterol, non-esterified fatty acids (NEFA) and triglycerides) at each visit. Samples for these measurements were frozen at –20°C and analysed at one central laboratory. The results were not made available to investigators during the study. Body weight, height, blood pressure, and heart rate were also recorded and body mass index (BMI) calculated. Blood pressure was recorded using a standard sphygmomanometer after 5 min resting supine. A 12-lead electrocardiogram (ECG) was recorded at screening, baseline, week 2, and week 12. The screening ECG was examined by the investigator before the patient was randomized to treatment. In addition, this and all subsequent ECGs were assessed by an independent cardiologist.

All adverse events, including date of onset, severity, duration and outcome, and the likely relationship to treatment were recorded, whether or not the investigator considered them to be causally related to treatment. Samples for routine clinical blood chemistry, haematology, and urinalysis were obtained at each visit to monitor safety and these results were available to investigators during the study. Patients whose fasting capillary blood glucose rose above 15 mmol $l^{-1}$ were reviewed again within a few days and if still high they were withdrawn from the study to avoid prolonged severe hyperglycaemia.

### *Analytical Methods*

All assays were performed at the West Middlesex Hospital Laboratory. Initially, total $HbA_{1c}$ was measured using an automated affinity chromatography method (Abbott Vision Glycated Hb test No. 3A32, Chicago, Ill., USA). The inter-assay coefficient of variation was 4% and the reference range was 4.1–5.7 %. The assay for $HbA_{1c}$ was changed inadvertently during the course of the study from the Abbott to the Glycomat assay (CIBA Corning,



 

London, UK). $HbA_{1c}$ data are therefore not presented in this report. All other assays were performed as described previously.[10]

Measures of insulin sensitivity and beta-cell function were derived from fasting glucose, insulin, and C-peptide data using the homeostasis model assessment (HOMA) mathematical model as described previously.[10]

### *Statistical Analysis*

The primary assessment of efficacy was glycaemic control as measured by fasting serum glucose after 12 weeks' treatment. After the start of the study, but prior to statistical analysis, the primary endpoint was changed from $HbA_{1c}$ because the assay technique was changed inadvertently during the study and the two methods were not equivalent. However, at the two-sided 5 % significance level, the study had 80 % power to detect a 10 % decrease in $HbA_{1c}$ on any dose regimen of troglitazone compared with placebo.

The data were analysed on an intention-to-treat basis on all randomized patients who took at least one dose of study medication and who provided a baseline assessment and at least one post-baseline assessment. All analyses were performed using a last-visit-carried-forward approach, carrying forward the last non-missing, post-baseline assessment for patients withdrawing from the study. In addition, analyses were repeated using only data recorded at week 12. With the exception of insulin sensitivity and beta-cell function, a log transformation was applied to the laboratory data prior to analysis.

All parameters were analysed using analysis of covariance (ANCOVA) allowing for country, baseline, and treatment. In each analysis, the primary comparisons were of each dose regimen with placebo, though secondary comparisons of once- and twice-daily dose regimens were also performed for interest. For each primary comparison, the ratio between each dose regimen and placebo was obtained together with a 95 % confidence interval and tested for significance at the two-sided 5 % level. These comparisons used the overall error from the ANCOVA. The statistical analysis was performed using SAS® version 6.08 systems and procedures.

## Results

Ninety-three of the 229 patients treated with study drug were male, mean age was 75 (range 69–85) years and mean duration of diabetes was 9 (range <1 to 48) years. The mean BMI was $26.9 \pm 3.9$ kg $m^{-2}$ for males and $27.6 \pm 4.7$ kg $m^{-2}$ for females. The treatment groups had similar distributions of characteristics and fasting serum glucose at baseline. One hundred and sixty-one patients (70 %) had been treated with oral antidiabetic agents (OADs) during the 3 months prior to entry into the study. The remaining patients had been treated with diet alone. The proportions of patients receiving pre-study OADs were similar in all groups (troglitazone: 400 mg once daily, 74 %; 200 mg twice daily, 72 %; 800 mg once daily, 63 %; 400 mg twice daily, 60 %; placebo, 80 %). Pre-study medications included acarbose, sulphonylureas, and metformin. The intention-to-treat population comprised 224 patients: 5 patients were excluded because of failure to provide any post-baseline efficacy data. Sixty-five patients (28.3 %) withdrew during the course of the study, 43 of these due to adverse events. In the analysis of fasting serum glucose after 12 weeks' treatment, 20–33 % of patients had data carried forward (troglitazone 20–25 %, placebo 33 %).

### *Effect on Metabolic Parameters*

Adjusted geometric mean fasting serum glucose was significantly lower for troglitazone dose groups than for placebo (18–26 % lower) after 12 weeks' treatment (Table 1, Figure 1). The time course for the onset of this effect was rapid, with a statistically significant difference between treatment and placebo groups after 1 week. Apart from those receiving the 400 mg once-daily dose, patients receiving troglitazone treatment also had significantly lower fructosamine at 12 weeks compared to those receiving placebo (Table 1, Figure 1). The adjusted geometric mean fructosamine values for troglitazone-treated groups were 5–15 % lower than for the placebo group, while insulin and C-peptide concentrations were also significantly lower in all treatment groups at week 12 (Table 1, Figure 1). Indices of both insulin sensitivity and beta-cell function were significantly improved at all doses of troglitazone at week 12 (Table 1). Reductions in glycaemic parameters compared to placebo were still apparent at follow-up, 10–14 days after the end of the study.

Fasting serum glucose data were re-analysed to examine consistency of effect across various patient factors. There was no significant difference in the response to troglitazone between males or females. In the placebo-treated patients, fasting serum glucose rose to a greater extent in patients previously treated with oral hypoglycaemic agents (11.8 mmol $l^{-1}$ at baseline to 13.6 mmol $l^{-1}$ at week 12) than in those treated with diet alone (from 9.5 to 10.0 mmol $l^{-1}$). There was, however, no significant difference in response to troglitazone between patients treated previously with diet alone or oral hypoglycaemic agents.

Total cholesterol was significantly higher with the troglitazone 400 mg once-daily dose, but not at the other doses, compared with placebo (Table 2). LDL-cholesterol (calculated) also showed a slight increase in those patients receiving troglitazone once daily (Table 2). No difference was observed in HDL-cholesterol concentrations between troglitazone and placebo. The LDL/HDL ratio did not change significantly, except in the 400 mg once-daily group. Serum NEFAs and triglycerides were lower in all troglitazone-treated groups (Table 2, Figure 1).

For all parameters, there was no evidence of a

Table 1. Comparison of parameters of glucose metabolism for the different treatment groups at baseline and week 12 (geometric means)

| | Placebo | 400 mg od | 200 mg bd | 800 mg od | 400 mg bd |
|---|---|---|---|---|---|
| Number of patients | 45 | 45 | 54 | 40 | 40 |
| Fasting glucose (mmol $l^{-1}$) | | | | | |
| baseline | 11.3 | 11.4 | 12.1 | 10.6 | 10.1 |
| week 12 | 12.9 | 10.2[c] | 11.1[c] | 9.0[c] | 8.7[c] |
| Fructosamine ($\mu$mol $l^{-1}$) | | | | | |
| baseline | 370 | 364 | 391 | 364 | 358 |
| week 12 | 405 | 376 | 393[a] | 340[c] | 354[b] |
| Insulin (mU $l^{-1}$) | | | | | |
| baseline | 11.2 | 11.4 | 10.7 | 10.9 | 10.4 |
| week 12 | 12.7 | 9.4[c] | 8.5[c] | 8.2[c] | 8.3[c] |
| C-peptide (ng $ml^{-1}$) | | | | | |
| baseline | 2.68 | 2.35 | 2.09 | 2.28 | 2.13 |
| week 12 | 2.71 | 2.16[a] | 1.83[c] | 1.98[c] | 1.67[c] |
| Insulin sensitivity (%) | | | | | |
| baseline | 30.4 | 29.1 | 30.8 | 31.0 | 33.8 |
| week 12 | 27.5 | 35.6[c] | 37.7[c] | 42.9[c] | 43.6[c] |
| Beta-cell function (%) | | | | | |
| baseline | 33.8 | 30.5 | 25.9 | 39.1 | 33.9 |
| week 12 | 29.9 | 34.3[a] | 30.9[b] | 44.5[c] | 40.5[c] |

[a]$p<0.05$, [b]$p<0.01$, [c]$p<0.001$ compared to placebo after adjustment for baseline value and any difference; od, once-daily dosing; bd, twice-daily dosing.

difference between twice-daily dosing and equivalent once-daily dosing. The analyses were repeated including only patients with evaluable data at week 12. The results were consistent, showing that carrying data forward had no effect on the overall results.

### *Other Analysis*

There was no significant change in body weight, BMI or waist/hip ratio in the troglitazone- or placebo-treated groups.

### *Side-effects*

Troglitazone was well tolerated and there was a similar incidence of adverse events in the troglitazone treatment groups (46–65 %) relative to the placebo group (59 %). There were no clinically important changes in heart rate, blood pressure or ECG over the 12-week treatment period. There were no reports of symptomatic hypoglycaemia in any of the patients, and there were no major clinically significant adverse effects on biochemical and haematological parameters. Although transient decreases in neutrophil and lymphocyte counts were seen these differences were not statistically significant (Fisher's exact test). No clinical symptoms resulted from these changes. No effect on total white cell count was observed since changes in neutrophil counts were accompanied by reciprocal changes in lymphocyte counts. Four to 11 % of troglitazone-treated patients compared with 13 % of patients in the placebo group had a liver function parameter over twice the upper limit of normal at any time after the start of treatment. Mainly, elevations in $\gamma$GT were observed in the placebo group while changes in AST and ALT were more evident in troglitazone-treated patients, particularly in the 800 mg and the twice-daily regimens. One patient receiving troglitazone (400 mg twice-daily) experienced rises in AST and ALT, after 1 week of treatment, which were considered moderate adverse events and led to withdrawal. In addition this patient also experienced malaise and vomiting. AST (normal range 0–18 U $l^{-1}$) rose from 9 U $l^{-1}$ at baseline to 25 U $l^{-1}$ at week 1 and returned to 10 U $l^{-1}$ at follow-up. ALT (normal range 0–24 U $l^{-1}$) increased from 11 U $l^{-1}$ at baseline to 36 U $l^{-1}$ and 39 U $l^{-1}$ at week 1 and follow-up, respectively.

A total of 65 patients (28.3 %) in the study population withdrew after randomization, two-thirds (43) due to adverse events mainly related to lack of efficacy or gastrointestinal symptoms. The proportion of patients experiencing adverse events leading to withdrawal was similar for troglitazone-treated (13–24 %) and placebo groups (20 %). Fourteen patients (6.1 %) withdrew from the study due to hyperglycaemia. The incidence of withdrawal for this reason was similar in troglitazone- (2.5–7.4 %) and placebo-treated (6.5 %) groups.

## Discussion

Type 2 diabetes mellitus is a common condition in the elderly, affecting 9–18 % of those aged over 65 years.[13–15] Few studies have specifically addressed the effects of oral hypoglycaemic agents in the elderly, who now constitute about 40 % of all diabetic patients. In this study we have shown that a degree of control of hyperglycaemia can be achieved in elderly patients, without the risk of hypoglycaemia, with troglitazone, a novel insulin action enhancer. The majority of patients in all treatment groups were taking conventional oral anti-diabetic agents prior to entering the study and,



 

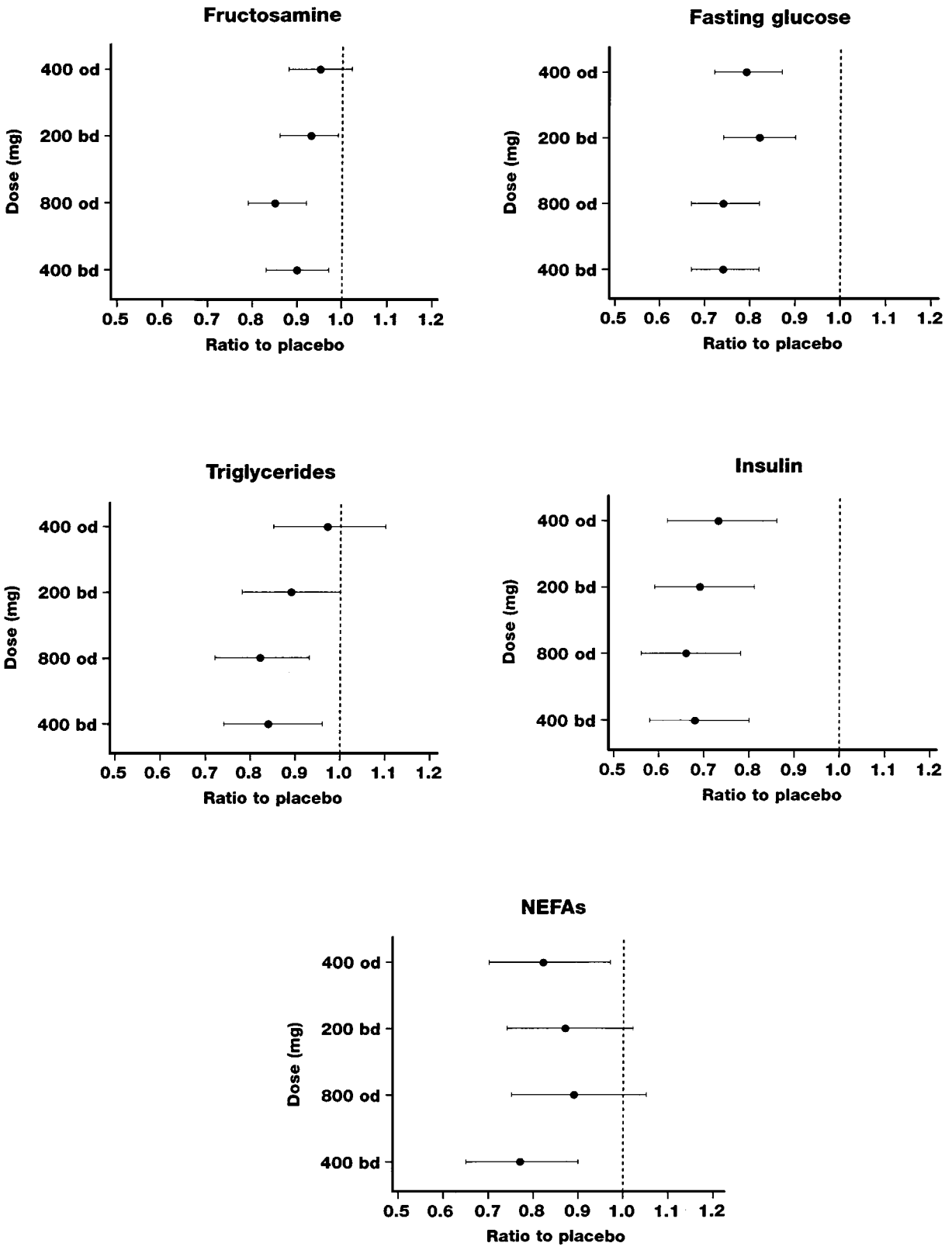


Figure 1. Effect of troglitazone on glycaemic and lipid parameters at week 12. Ratio of effect of each dose compared to placebo: mean and 95 % confidence intervals (adjusted for baseline and difference between countries); od, once daily; bd, twice daily

therefore, glycaemic control worsened during treatment with placebo. In contrast, glycaemic control was maintained at all doses of troglitazone from as early as 1 week after treatment initiation to the end of the study period. Fasting serum glucose was ≥18 % lower compared to placebo after 12 weeks' treatment, even at the lowest dose studied. No significant dose–effect relationship was observed over the doses examined in

Table 2. Lipid profile at baseline and after 12 weeks of trial medication (geometric means)

| | Placebo | 400 mg od | 200 mg bd | 800 mg od | 400 mg bd |
|---|---|---|---|---|---|
| Number of patients | 45 | 45 | 54 | 40 | 40 |
| Total cholesterol (mmol $l^{-1}$) | | | | | |
| baseline | 6.1 | 6.4 | 6.7 | 6.1 | 5.9 |
| week 12 | 6.1 | 6.8[b] | 6.8 | 6.3 | 6.0 |
| HDL-cholesterol (mmol $l^{-1}$) | | | | | |
| baseline | 1.14 | 1.13 | 1.16 | 1.19 | 1.12 |
| week 12 | 1.18 | 1.17 | 1.22 | 1.30 | 1.18 |
| LDL-cholesterol (mmol $l^{-1}$) | | | | | |
| baseline | 3.9 | 4.0 | 4.5 | 3.9 | 3.8 |
| week 12 | 3.8 | 4.4[b] | 4.6 | 4.2[a] | 3.9 |
| LDL/HDL ratio | | | | | |
| baseline | 3.4 | 3.5 | 3.9 | 3.3 | 3.3 |
| week 12 | 3.2 | 3.7[a] | 3.7 | 3.2 | 3.3 |
| Triglyceride (mmol $l^{-1}$) | | | | | |
| baseline | 1.82 | 2.17 | 1.92 | 1.88 | 1.68 |
| week 12 | 1.89 | 2.07 | 1.74[a] | 1.59[b] | 1.51[a] |
| NEFA (mmol l−1) | | | | | |
| baseline | 0.63 | 0.75 | 0.69 | 0.59 | 0.60 |
| week 12 | 0.67 | 0.60[a] | 0.61 | 0.57 | 0.50[b] |

[a]$p<0.05$, [b]$p<0.01$, [c]$p<0.001$ compared to placebo after adjustment for baseline values and any differences between countries.
NEFA, non-esterified fatty acids; od, once-daily dosing; bd, twice-daily dosing.

this study. Reductions in serum fructosamine and fasting serum glucose were of a similar magnitude to those described previously.[10] The similar efficacy and safety profiles in this elderly group of Type 2 diabetes patients were achieved with comparable drug concentrations to the younger population, therefore suggesting that troglitazone has predictable pharmacology, irrespective of age. Dividing the daily dose and giving it twice daily was no more effective or better tolerated than the equivalent once-daily dose.

Both increasing insulin resistance and declining beta-cell function with advancing age are implicated in the progression of diabetes in the elderly.[16] Premature beta-cell failure, due to increased demands on beta cells resulting from insulin resistance, may be important in the pathogenesis of diabetes in such cases. Reducing insulin resistance may, therefore, help preserve beta-cell function and possibly postpone the need for insulin treatment. Improvement in glycaemic control observed during troglitazone treatment in our elderly patients was achieved with a reduction in endogenous insulin secretion. HOMA analysis confirmed a significant improvement in insulin sensitivity with all doses of troglitazone used. An improvement in beta-cell function was also noted, but this is likely to have occurred as a secondary phenomenon following improvement in insulin sensitivity and fasting glucose.[17] Troglitazone has been shown to improve insulin sensitivity in patients with impaired glucose tolerance in whom this agent may help to preserve beta-cell function.[18] Thus, troglitazone may be particularly useful early in the course of the disease. In patients whose hyperglycaemia is not controlled by troglitazone alone, combination therapy with other oral anti-diabetic agents may be required. Further studies are needed to assess the safety and efficacy of troglitazone when given with other agents such as sulphonylureas.

Troglitazone is a potent activator of peroxisome proliferator activated receptor gamma (PPARγ), a nuclear hormone receptor important in adipogenesis, suggesting that its anti-lipolytic effects may be important to its mechanism of action.[19,20] High concentrations of circulating NEFAs may cause insulin resistance in Type 2 diabetes by inhibiting the uptake and utilization of glucose and its reduction has been shown to lead to improvement in glucose tolerance and insulin sensitivity.[21] Thus, the observed reduction in serum NEFAs during troglitazone treatment may contribute to a further improvement in glucose tolerance. The changes in lipid profile, including reduction of serum triglyceride and NEFAs, are consistent with data from the previous studies.[7–10] As in a previous study, a tendency to a rise in total and LDL-cholesterol with some doses of troglitazone was observed, although the significance of this finding is unclear and requires further investigation. Fibrates, which activate the PPARα receptor, have also been shown to increase LDL-cholesterol in diabetic patients; this increase is thought to be due to an increase in LDL particle size.[22]

Adverse events during treatment with troglitazone were similar to those seen in patients receiving placebo. In this elderly population troglitazone treatment was not associated with hypoglycaemia. These results are consistent with previous reports.[7–11] Since the mode of action of this drug is to enhance tissue sensitivity to insulin,[7–10,18] concentrations of endogenously secreted insulin fall appropriately, thus avoiding hypoglycaemia. It is also significant that there was no increase in weight observed during troglitazone treatment. Although transient



 

decreases in neutrophil counts were reported in previous studies,[10,11] in the present study reductions in neutrophil counts were accompanied by reciprocal elevations in lymphocytes and total white cell count remained within the reference range. The overall effects on glycaemia, insulin concentrations and lipids, together with good patient tolerability of troglitazone, appear to compare favourably with those of sulphonylureas, metformin or acarbose.[3,23,24] Post-marketing surveillance of patients receiving troglitazone worldwide has shown cases of liver dysfunction. Disturbances in liver enzymes were observed in some patients in the study and one patient was withdrawn for this reason.

Thus, the results of the present study indicate that troglitazone is an effective and reasonably well-tolerated drug for treatment of Type 2 diabetes in the elderly. These findings are consistent with those observed in younger patients.[10] It should also be noted that improved control of hyperglycaemia was achieved in this elderly group of patients without weight gain or hypoglycaemia, and improvements in insulin sensitivity were associated with potentially beneficial effects on hyperlipidaemia and hyperinsulinaemia.

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